DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE OPEN SESSION

67th Meeting

Thursday, June 7, 2001
8:15 a.m.

Holiday Inn Bethesda Versailles Ballroom
8120 Wisconsin Avenue Bethesda, Maryland

PARTICIPANTS

Stacy Nerenstone, M.D., Chair
Karen M. Templeton-Somers, Ph.D., Executive Secretary

MEMBERS

Kathy S. Albain, M.D.
Douglas W. Blayney, M.D. John T. Carpenter, Jr., M.D.
Stephen George, Ph.D.
David P. Kelsen, M.D.
Donna Przepiorka, M.D., Ph.D.
Bruce G. Redman, D.O.
Victor M. Santana, M.D. George W. Sledge, Jr., M.D. Sarah A. Taylor, M.D.
Jody L. Pelusi, F.N.P., Ph.D., Consumer Representative

GUESTS AND GUEST SPEAKERS (Non-Voting)

Steven D. Averbuch, M.D.
Carl F. Dixon
Robert Erwin
Ruth Linden, Ph.D. Jan Platner
Robert Spiegel, M.D.

FDA

Dr. Robert Temple Dr. Richard Pazdur Dr. Grant Williams Dr. Patricia Keegan
Ms. Patricia Delaney

C O N T E N T S

P R O C E E D I N G S

Call to Order and Opening Remarks

DR. NERENSTONE: Good morning. First of all, I would like to thank everyone for coming to ODAC. This morning we are going to be discussing the single patient use of non-approved oncology drugs and biologicals.

I would like to start with the introduction of the committee, and if we could go around and have everybody state their name and where they are from into the microphone for the record, please. We will start with Dr. Averbuch.

Introduction of the Committee

DR. AVERBUCH: Steve Averbuch, Astra/Zeneca Pharmaceuticals.

DR. SPIEGEL: Bob Spiegel, Schering-Plough.

DR. LINDEN: Ruth Linden, UC/San Francisco and UC/Berkeley, University of California.

MS. PLATNER: Jan Platner, National Breast Cancer Coalition.

MR. ERWIN: Robert Erwin, Marti Nelson Cancer Research Foundation.

DR. BLAYNEY: Doug Blayney, Wilshire Oncology Medical Group. Pasadena, California.

DR. KELSEN: Dave Kelsen, Sloan-Kettering, New York.

DR. PELUSI: Jody Pelusi, Phoenix Indian Medical Center and the Consumer Rep.

DR. TAYLOR: Sarah Taylor, University of Kansas.

DR. NERENSTONE: I am Stacy Nerenstone, Medical Oncology, Hartford Hospital.

DR. TEMPLETON-SOMERS: Karen Somers, Executive Secretary to the committee, FDA.

DR. GEORGE: Stephen George, Duke University.

DR. SLEDGE: George Sledge, Indiana University.

DR. REDMAN: Bruce Redman, University of Michigan.

DR. PRZEPIORKA: Donna Przepiorka, Cell and Gene Therapy, Baylor College of Medicine, Houston.

DR. CARPENTER: John Carpenter, University of Alabama at Birmingham.

DR. ALBAIN: Kathy Albain, Medical Oncology, Loyola University, Chicago.

DR. WEISS: Karen Weiss, Center for Biologics, FDA.

DR. WILLIAMS: Grant Williams, Center for Drugs, FDA.

MS. DELANEY: Pattie Delaney, Office of Special Health Issues, Cancer Liaison Program, FDA.

DR. PAZDUR: Richard Pazdur, FDA.

DR. TEMPLE: Bob Temple, Office Director, OD-1, FDA.

DR. NERENSTONE: Thank you. Dr. Templeton-Somers will now discuss the Conflict of Interest Statement.

Conflict of Interest Statement

DR. TEMPLETON-SOMERS: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Since the issue to be discussed by the committee at this meeting will not have a unique impact on any particular firm or product, but rather may have widespread implications with respect to an entire class of products, in accordance with 18 U.S.C. Section 208(b), waivers have been granted to all members and consultants who have reported interests in any pharmaceutical companies.

A copy of these waiver statements may be obtained by submitting a written request to the FDA's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

With respect to the FDA's invited guests, there are reported affiliations which we believe should be made public to allow the participants to objectively evaluate their comments.

Ruth Linden, Ph.D., would like to disclose for the record that she has provided consulting services for MGI Pharma regarding the development of an expanded access program. This service was provided January 2001 through February 2001 and may resume in the future. Her views on expanded access are described in the paper she presented at the December 2000 meeting of the Oncologic Drugs Advisory Committee.

Robert Erwin would like to disclose that he is founder, shareholder, and full-time employee of a large scale biology corporation. The firm is conducting research in medical fields including oncology.

Robert Spiegel, M.D., would like to disclose that he is the Senior Vice President of Medical Affairs and Chief Medical Officer of

Schering-Plough.

Steven Averbuch, M.D., would like to disclose that he is Senior Medical Director, Oncology, of Astra/Zeneca Pharmaceuticals and holds stock in Astra/Zeneca, Merck, and 3-Dimensional Pharmaceuticals.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous involvement with any firm whose products they may wish to comment upon.

Thank you.

Open Public Hearing

DR. NERENSTONE: We would like to start the next part, which is the open public hearing.

Karen Doran.

MS. DORAN: Good morning. I wish to thank the FDA for giving me another opportunity to address the Oncologic Drug Advisory Committee about the Gene Therapy Clinical Trial. For those who

were not in attendance at the December 2000 meeting, let me briefly explain why I am here today.

My mother, Hazel Doran, had been approved to participate in the Gene Therapy Clinical Trial at the University of Pennsylvania in Philadelphia. She was well informed of the risks and benefits and decided gene therapy was her only hope in her fight against mesothelioma, a deadly form of lung cancer.

My mother was a non-smoker and was exposed to asbestos as a young adult. Upon the death of a young man from Arizona who was undergoing gene therapy, the FDA put a hold on any further gene therapy clinical trials. This prevented my mother from her only chance at a possible cure, and as we waited hopefully for her treatment to begin, over a three-month period, mother did not partake of any type of cancer therapy.

We finally found out about gene therapy being put on hold through the news media. No one at the medical center informed us of this momentous decision.

I am here today as an advocate for patients considering any clinical trial, the right to decisions, choice, and being informed.

Consider for a moment that you have a loved one missing in action during a war. You may never know if they are dead or alive. This is how my family feels. We will never know if the Gene Therapy Clinical Trial would have saved or extended my mother's life. That question will stay with us for the rest of our lives.

My mother was willing to take this chance, not only for herself, but for others, as well. She had hoped in addition to keeping her alive that medical science would also learn something from her gene therapy treatment that in turn might save someone else's life. That is why it is so important that those wanting to be a part of any clinical trial should have the opportunity to do so.

It is hard for me to understand how someone could decide to halt a clinical trial when there have been proven benefits and it is the only hope for a terminally ill person, like my mother. My mother, age 72 at the time, was active and involved with her family and community. She was determined to live.

When I spoke in December, someone said they could not understand how I could make this

presentation so soon after my mother's death. It is because of my mother that I have this strength. She instilled in me the right to stand up for what you believe. My family and I believe that cancer patients, along with their physicians, should have the right to decide if a clinical trial is right for them.

Isn't everything we do in life a trial? At one point, taking an aspirin was a trial as well as chemotherapy.

My family and I, on behalf of my mother, Hazel Doran, strongly encourage the Gene Therapy Clinical Trial to be reinstated. When a person is told they are going to die and that they might benefit from a clinical trial, they should have a choice.

When my mother was told she could not participate in this Gene Therapy Clinical Trial, all hope was taken from her. We could see an immediate change in her outlook on fighting this horrible disease. Even though mom put up a tremendous effort, she was finally defeated by the cancer because someone took away her right to decide what treatment options she had.

In the last remaining months of my mom's

life, there was very little we could do for her. However, one bright spot was her 72nd birthday. Have you ever given a birthday party for someone who is dying? It was probably the best thing we could have done for mom. It gave her friends the opportunity to visit her, wish her a happy birthday, and that is how they now remember my mother - in a very positive manner celebrating another year of life.

Please consider carefully when deciding if this Gene Therapy Clinical Trial should be permitted to begin at the University of Pennsylvania in Philadelphia. Think of my mother and think of someone else's loved one and the only possible hope that they have in fighting this rare deadly form of lung cancer.

Please consider carefully that this decision could mean someone celebrating another birthday with their family. My mother's birthday passed this year - we honored her by placing flowers on her grave. We would have rather placed them in her hands.

Please consider the right for a patient to decide what is best for them when fighting deadly disease. Your decision may help prevent another

family from spending the rest of their lives asking What If?

Thank you.

DR. NERENSTONE: Thank you very much, Ms. Doran.

Susan Weiner.

MS. WEINER: Thank you for the opportunity to speak to the FDA Oncologic Drug Advisory Committee on this important issue.

I am Susan Weiner, President and Founder of the Children's Cause, a patient and family led education and advocacy group dedicated to improving outcomes for childhood cancer. I was also the mother of Adam Weiner, who lived and died with a brain tumor.

I addressed this group briefly in December and am grateful for the chance to speak again. At that time, I emphasized the Children's Cause position on single patient use in children, that it should be unnecessary. We argued for the ideal that there should be a comprehensive, tightly organized, and proactive national clinical trials program through the Children's Oncology Group, so that any child with cancer might qualify for an open trial.

Single patient use of non-approved drugs represents a special threat in pediatric oncology because treatment outside of a clinical trial is not consistent with the high quality care that has saved so many children's lives. It is also a threat because children with cancer are a precious and scarce resource from which we must learn how to improve treatment for others.

I support this position because I believe it is best for children struggling with cancer and those yet to be diagnosed, but I wanted to speak today about what so-called compassionate use was like from my own personal perspective, to highlight the conflict from the other side. It is still very difficult for me to talk publicly about my son Adam's experience even these many years later, so forgive me.

Adam was never expected to live beyond his brain tumor diagnosis in infancy, but live he did until he was nearly 14 years old. Three months before Adam died, he experienced among other things status epilepticus. For many, many days he had constant uncontrollable seizures. His doctors from one of the nation's best academic medical centers discussed applying for what they called

compassionate use of a drug that might stop the seizures. A few days later they told me that it was not possible for him to have access to this experimental anticonvulsant.

I neither knew what made him eligible nor ineligible, nor what process was necessary to obtain the drug. The impact was clear, however, hope of ending this nightmare had been introduced with language that conveyed sensitivity to our desperate circumstances, only to be withdrawn for reasons that were not clear, and when access that could be considered compassionate was no longer possible, all hope and options were gone.

The issues of language, terminology, consistency, and communication were at the heart of much of the misunderstanding and distress that parents and patients have about access to new drugs in clinical research. The unfortunate term "compassionate use" needs to be dispensed with entirely. FDA documents no long use the phrase, but it still appears in the NCI document on non-research use of investigational agents.

The phrase persists among physicians and families as a code phrase for our best hope, but it is a misnomer. There are other terms in current

use in FDA and NCI materials that need replacing and clarification.

For example, FDA's background materials for this meeting cite investigational use versus treatment use of investigational drug. Treatment presumes that a drug is known to be therapeutic. Drugs considered for single patient use are all investigational and therefore have unknown therapeutic effect.

Clinical trials are also always investigational, research, and not treatment, according to the consent forms that we sign. So, how can giving an investigational drug with unknown therapeutic effect be treatment when it is used for a single patient, but not treatment when it is used in the context of a clinical trial?

Clearly, there is need for linguistic overhaul both at the FDA and the NCI in the description of single patient use. Beyond terminology, however, FDA and NCI need to adopt open and consistent rules and policies on single patient use.

The National Cancer Institute sets the policies, standards, and procedures for the conduct of clinical trials through the National Pediatric

Cooperative Groups. If these are indeed the best ethical and scientific strategies to guide children's access to new oncology drugs, then, they should apply equally to access through clinical trials, special exception, and single patient use for children.

For families seeking care, clarity, consistency, and access to information in this complex domain are vital to making sound and rational decisions for our children. Accordingly, we make the following recommendations.

FDA and NCI should coordinate efforts to develop a common, nonvalue-laden set of terms with clear and precise definitions to describe single patient use. FDA and NCI should develop consistent, open, and publicly accessible policies about single patient use. Such an approach can avoid unequal access to new drugs and help preserve the clinical trial system.

To implement these changes, FDA and NCI should coordinate a communication strategy for print and electronic materials to educate and change public and professional perception about so-called compassionate use.

We applaud the FDA for holding these

meetings and for allowing an in-depth look at these important issues.

Thank you.

DR. NERENSTONE: Thank you very much for your thoughtful comments.

Helen Schiff.

MS. SCHIFF: Good morning. My name is Helen Schiff. I have no conflict of interest. I am a member of SHARE, a self-help group for women with breast or ovarian cancer based in New York City.

Today, I am speaking for SHARE members who have graduated from Project LEAD, a breast cancer advocacy training course. We meet monthly to discuss controversial issues facing women with breast cancer. I will present the evolution of our group's thinking on access to unproven drugs at three long intense meetings.

At our first meeting, most members of our group expressed total disbelief at the idea that advocates could be against single patient protocols, how could SHARE deny a dying woman the right to an unproven drug, SHARE should not close off any avenues of hope even false hope.

About one-third of our 20-member group

have metastatic breast cancer. At our next meeting we discussed the importance of not doing anything that would undermine the clinical trial system. We were all aware of the high dose chemotherapy fiasco, how lives can needlessly be cut short and how valuable time in which treatment advances can be made is wasted when experimental treatment is given outside of trials.

Still, the majority of our group felt that there must be a way to allow the use of unproven drugs that would not undercut the clinical trial system.

Next, we saw a videotape of a Sixty Minute segment which interviewed two women with advanced colon cancer. Both were trying to get the experimental drug C225. Neither of them qualified for the clinical trial. The both spent hours searching online, writing letters, and calling influential people.

In the end, the woman who devised the strategy of phoning the president of the drug company before his secretary was there to screen his calls got the drug. The woman who wrote to the President of the United States did not.

Jane Sawyer, a member of our LEAD group,

who had been metastatic for four years sent me a note saying I am convinced. She said it was painful to watch what those women went through. The results were unfair. I would rather be in a lottery.

Most of us then agreed that single patient protocols are anything but compassionate. They are very unfair and arbitrary and discriminate against people who are not highly educated or well connected.

At our final meeting, we came to a consensus that the real problem was with the clinical trial system itself. We need more high quality trials using novel agents. We need more access and faster enrollment. We need to test drugs in earlier stages of disease and later stages of disease, and in case of the new biologics, with and without chemotherapy.

We think any attempt to use access to unproven drugs is a way around the shortcomings of the clinical trial system will ultimately be a huge disservice to cancer survivors because trials are the only way to know if a new drug is better, no different, or worse than the standard of care.

We agreed that expanded access, not single

patient protocol, is the only fair way to provide access to unproven drugs and that it should be encouraged only: one, when the drug has exceptional promise due to very strong evidence in humans, not just good PR or elegant-sounding hypotheses; two, when it has a good safety profile; and, three, when the person does not qualify for any other high-quality trial.

A member of SHARE, who is an ovarian cancer survivor, at our meeting argued against this proposal, stating that ovarian cancer patients have fewer choices and need broader access to unproven drugs.

Speaking for myself, from what I know about Gleevec, that is a good example of the kind of exceptional drug we are talking about that should be, and was, made available by expanded access. I can't think of any others including Herceptin, that would fit into that category.

Gleevec's use, first in trials of CML leukemia and then for a rare form of intestinal cancer, speaks to the question raised by those with less common cancers. More and more we are looking at therapies, not by organ, breast, ovary, colon, et cetera, but by mutation, HER2, ras, EGFR, et

cetera.

Isn't it more rational and compassionate to set up different trials in other cancers with the same mutation than to give it to people who have little chance of benefiting from it? Isn't it more rational if extra drug is available to set up trials in later or early stages of disease, so we can actually learn something?

Are the drug companies being forced to give out unproven drugs for fear of bad PR, like the insurance companies were forced to pay for high-dose chemotherapy outside of trials?

We have too few people entering clinical trials. FDA and ODAC need to formulate a policy that will not undercut the clinical trial system. That is what is best for the interest of present and future cancer patients.

This is a statement of SHARE's Project Lead group. SHARE itself is still formulating its position.

DR. NERENSTONE: Thank you very much.

The next comments will be in the form of a letter from Dr. Queimado. Dr. Templeton-Somers will be reading.

DR. TEMPLETON-SOMERS: This letter is from

Lurdes Queimado, who is a lymphoma advocate.

"Dear Sirs and Madams: I am a founding member of the Lymphoma Action Alliance, an advocacy group created to help lymphoma patients gain access to the best and least toxic cancer treatments - when they are most likely to be effective. Professionally, I am an M.D./Ph.D., working full time in cancer research.

In low-grade Non-Hodgkin's lymphoma patients, chemotherapy and/or radiotherapy are relatively effective in temporarily reducing the patient's tumor burden. However, these therapies do not cure the disease, nor do they increase the overall survival. Therefore, chemotherapy and/or radiotherapy should not be considered standard treatments for this disease.

Indeed, this fact is recognized by every lymphoma specialist. For example, Dr. Dan Long, working at the NCI, wrote recently, "A patient with follicular lymphoma might hear from his or her physician treatment recommendations ranging from high-dose chemotherapy with stem cell transplantation to doing nothing and every gradation in between.

Patients with low-grade non-Hodgkin's

lymphoma understand the significant short- and long-term risks associated with chemotherapy and radiation, which include secondary malignancies, myelosuppression, organ dysfunction (cardiac, pulmonary and endocrine), neuropsychological effects, and degraded quality of life.

They know that the benefits will be short-lived and that repeated and increasingly less effective retreatments will be needed to control the disease. Based on this, patients with low-grade NHL often seek clinical trials as front-line therapy, but they often find that these trials are closed to previously untreated patients. Single patient exemptions are also systematically refused for these patients.

The reasons for this may be the widely accepted belief that all cancer patients should first receive the standard therapies and only when these therapies fail should they look for a clinical trial. It is illogical to apply this rule to low-grade NHL patients for the following reasons:

1. The approved therapies are not curative.
2. Approved therapies have known and

serious short- and long-term side effects.

3. These therapies can cause permanent damage, undermining the patient's ability to benefit from emerging therapies, such as vaccines and monoclonal antibodies.

4. Emerging therapies often attack specific targets and are less toxic.

5. Standard therapies can be used later if needed.

Many thousands of low-grade NHL patients are diagnosed every year. The majority of these patients, based on the survival statistics, should be treated in clinical trials. Since these patients cannot be absorbed by the available clinical trials, they should be granted single patient exemptions in order to access the most promising treatments. However, as described above, they are generally refused admission into studies because they have not yet received all possible standard therapies first.

It is urgent that the FDA, working with activists and patients, develop policies to facilitate expanded access and single patient INDs while assuring that meaningful data is collected. It is also urgent that incentives are developed to

assure that drug companies will be willing to participate in expanded access and single patient INDs.

Finally, since cancer is a life-threatening disease, expanded access and single patient INDs should be made available as soon as a drug has been proven safe and has shown efficacy, as was done with AIDS drugs over ten years ago. Thank you.

Lurdes Queimado, M.D./Ph.D., Lymphoma Advocate."

A copy of her statement is available at the reception desk out there for those in the audience who want to see it, and she does have references cited.

The second letter was received late last evening from Sally Cooper of NABCO.

"Dear ODAC Committee Members: Good morning. I am the Director of Information Services for the National Alliance of Breast Cancer Organizations, a national nonprofit information and education resource since 1986.

I personally have no financial interest in any pharmaceutical, biotech, medical device, or trial management company, but NABCO does receive

unrestricted educational grants from several pharmaceutical companies.

In addition to my current position, I also bring some perspective from 11 years of working in the HIV/AIDS epidemic, often directly on issues of early access to investigational agents.

In that capacity, I have worked with the FDA, numerous companies and researchers on single agent access, treatment INDs, and the design, delivery and publicizing of a number of expanded access programs for people living with HIV and AIDS. I would like to thank you all for providing us with this opportunity to speak and thank you as well for taking the time and effort to initiate a broad discussion about this confusing area.

I would like to start with two observations.

One. Something that has always dogged these discussions is a lack of data. We tend towards anecdotes and seemingly common-sense statements, but without data, no ethnographic or detailed qualitative research about who is getting early access and why, who chooses and who refuses to go in a trial in the face of expanded access; how many INDs are granted for what indications;

what useful data has been collected through expanded access programs, et cetera.

The missing data is worrisome. It can be problematic to develop policy without an evidence-based understanding of what has been happening. The solution may not work well, or worse, it may result in unwanted ramifications that no one was able to foresee without a better initial understanding.

Thus, before any significant change in the current policy is enacted, we would ask for some quantitative and qualitative research to better understand what is truly problematic in this arena, and what is not.

Two. It is very important conceptually to separate expanded access programs from single patient compassionate use. For example, there is little data but much concern that expanded access may interfere with trial accrual. However, it is inconceivable that the small number of individuals getting compassionate use could seriously interfere with accrual, especially in light of the relatively small sized trials in advanced cancers.

One major difference is that expanded access is a program. Single patient compassionate

use is not a program. It is simply a mechanism or opportunity that companies, clinicians and patients sometimes use. Whether and how much we want to turn it into a process should be carefully thought out, as real questions of flexibility may be compromised.

When looking at single patient compassionate use, several areas of concern stand out.

One area is the possibility of causing more harm than good. These are investigational agents being offered to patients with advanced disease who have run out of conventional treatment options. Some argue what's the point since there is little reason, honestly, to expect much benefit in this setting? Doesn't the possibility of harm outweigh any possible good? What is the good faith in this?

In addition, how can we be sure that patients really understand the possibility of harm here? How good is the informed consent process when the stakes are so high, and so little is known about the compound? As noted, this situation may be worsened by the existence of embargoed information that would be useful for the clinician

and patient to know - although this is something surely we can fix with confidentiality agreements and the like.

Well, the folks who testified in December answered these questions rather well, I think - individuals with serious illness or rare diseases going about their lives, hoping for the possibility of extending their lives further, often having already paid their dues in one or more clinical trials - not exactly the picture of desperate, ill-informed people believing in a miracle cure.

I think the FDA has widely kept this door open in the face of extreme complexity of illness, and recognizing an ethical need not to simply close off all access. We do not know what may come down the pike, we cannot anticipate what someone may need access to, and rather than pretend to, this mechanism was created to allow for a discussion when the possibility arises that this may be a source of treatment.

Single patient access is not a program, but a negotiation because so much is not known either about the drug or how it may work in an individual patient. This discussion serves an important purpose, as a sort of discovery phase in

which all players can decide whether it is worth going forward or not.

This leads to another issue - equity. Others have discussed this at length and it is clearly already high on the FDA's list of concerns. We also lack data about this, and I would caution those who assume that it is solely the well connected who succeed in this area.

Facing a terminal diagnosis can have a profound energizing effect on families and individuals, and a number of folks fight for early access who would never have thought about doing anything like this before. It can be a deep educational and politicizing experience. But it is clearly unfair how randomly compassionate use occurs.

One solution calls for better public education (including for clinicians) about the existence and procedures of this mechanism. However, increased public awareness will only ease some but not much of the current inequity.

Compassionate use is a time-consuming, negotiated process that few medical centers will be able to offer. With our multi-tiered health care system, this means that folks with excellent

insurance or resources may have this access, and others with fewer resources probably will not.

Another approach to the problem of equity is to recognize that right now, too much is being asked of the compassionate use mechanism. Far too often, it's the only early access option, and filling in when expanded access programs should be considered.

Equity issues can and should be earnestly addressed through other early access mechanisms, such as expanded access and parallel track programs, administered through multiple venues such as the VA and public hospital systems, with national IRBs and shared staffing support, when the nature of the Phase II data, drug supply, safety and toxicity data and disease condition warrant such distribution. These options have been used in HIV, so we know they are possible. With many new compounds in the pipeline, it's time to make a broader social commitment to fair expanded access programs when prudent and feasible.

Finally, one area that we can all improve in is our communication with patients. It's time to let patients know what's going on. The doctor who fails to get the IRB paperwork in, the company

reluctant or unable to release drug, the FDA unsure of how to figure out the safety/efficacy profile, the community-based program overly excited by a press release - we are all part of the problem when we fail to tell patients our plans, our mistakes, what we really can do and what we can't.

It is always much easier to hear the truth and cope with it than get stonewalled. There are real supply problems, real safety issues, serious efficacy questions and always the real problem of time and resources to get things done well.

The more information that flows, the more we work together on building functional expanded access - the less resonant all the media hype will be. The recent 60 Minutes piece would have been very different if the company in question had early on held community meetings and made an effort to address a natural and understandable phenomena; folks interested in trying their drug had very limited options otherwise.

Single patient compassionate access serves as an important source of hope and sometimes access. It's an imperfect, necessary bridge between our urgently important but contradictory twin social goals of developing effective therapies

and providing care for the individuals that we as a society have failed to find answers for yet.

What I learned from the HIV epidemic was that we can't simply choose one goal over the other, but must face squarely the challenge of trying to accomplish both. It's time as a society to learn to be more realistic about what emerging therapies can offer us, which in turn will enhance the effectiveness of the informed consent process.

At the same time, we can also communicate better, all the players, so that where possible patients will be able to see and experience a society that is committed to providing equitable early access when prudent and possible. That brings us full circle to hope, that very human of emotions, which sustains all of us.

Thank you very much. Sally Cooper, Director, NABCO Information Services."

DR. NERENSTONE: Thank you, Karen.

I would like to turn now to the Summary of Regulatory and Industry Considerations.

Dr. Williams is going to lead the discussion.

Introduction

Summary of Regulatory and Industry Considerations

Grant Williams, M.D.

DR. WILLIAMS: Madam Chairman, Committee Members, ladies and gentlemen: In the next 20 minutes I will summarize presentations made by speakers from FDA, from the pharmaceutical industry at our last session on treatment use of investigational drugs.

[Slide.]

You will have to excuse the title. After that last speaker, I still have treatment in there, and unless we can come up with another name, I guess it is going to stay there for now.

[Slide.]

First, I will review the regulatory background that I presented for FDA, then, summarize the points on single patient use of investigational drugs made by Dr. Robert Spiegel from Schering-Plough, and finally, I will summarize the presentation on expanded access made by Dr. Gerard Kennealey from Astra/Zeneca.

We are very appreciative to Dr. Spiegel and Dr. Kennealey for providing such an instructive and honest view of how treatment use of

investigational drugs affects the pharmaceutical industry, and for providing us with ideas of how this process might be improved.

[Slide.]

Again, the objectives for this meeting are to educate the public on the issues surrounding the treatment use of experimental cancer drugs and, especially for this meeting, to get advice and input of when it is appropriate for FDA to allow experimental drugs to be used for treatment use of individual cancer patients.

Note that FDA has only a partial role, that is, defining the rough boundaries within which treatment use is appropriate. From discussions we heard from patients, discussions which were echoed by a TV spot on 60 Minutes about compassionate use a few weeks ago, it is clear there are other issues that are very important to patients, such as when should a company provide access to experimental treatment and how should the drug be distributed, so that patients are treated fairly.

We believe that these issues should be addressed in a consensus conference in the near future, a conference to include representatives from the two main parties - the pharmaceutical

industry and cancer patients and their advocacy groups.

We believe that the Food and Drug Administration and the National Cancer Institute can play important roles in facilitating this dialogue. When everyone agrees upon a set of norms for treatment use of experimental drugs, both patients and industry will benefit.

So, there is the framework for today. Today, we are asking when should FDA allow treatment use of experimental drugs.

[Slide.]

First, I want to review a few definitions that we talked about last time. All use of experimental drugs is regulated by FDA under an IND. An IND is an Investigational New Drug application.

There are several individuals involved in the process of an IND. First, there is the IND sponsor. The sponsor is the individual company or institution that assumes responsibility for overseeing the study, for assuring that the regulations are followed, and for reporting to FDA on the progress of the study. The sponsor may or may not be the manufacturer of the drug.

Next, there is the investigator. The investigator is that individual that actually performs the trial or administers the drug, and at times, and quite often in these circumstances, at least with single patient INDs, the investigator and the sponsor are the same person.

[Slide.]

The usual purpose of an IND is to allow for clinical investigations to determine whether a drug is safe and effective. If findings from the studies are favorable, the sponsor will then submit all of the data from these investigations to the FDA to determine whether the drug an be approved for marketing. In this way, the drug becomes widely available to the American public.

The FDA strongly endorses participation in clinical trials because it is in the best interest of the American public. It is in their best interest to determine whether a drug is safe and effective. Individual patients also benefit by participating in clinical trials.

The best treatments available are selected for these trials. However, there are times when it may be appropriate to make an investigational drug available primarily for treatment rather than for

the usual purpose of investigating safety and effectiveness.

[Slide.]

The terminology surrounding the treatment use of experimental drugs can be confusing because the regulations do not explicitly describe all of the practices. Different terms are frequently used for the same practices. Treatment use of experimental drugs may be divided into two main groups - single patient treatment use and expanded access treatment use, but these are not terms or programs described in the regulations. They are just useful descriptive terms.

Expanded access refers to multiple patients being treated under a single protocol. Single patient use, individual protocols or treatment plans are drawn up for each patient.

[Slide.]

Historically, there have been several different methods for providing expanded access. In the cancer area, since the 1970s, NCI has worked with the FDA to provide investigational drug under a mechanism called Group C. This mechanism was only for drugs provided by NCI.

In 1987, FDA developed an official program

described in the regulations called the treatment IND. That was for patients for any life-threatening disease, not just for cancer. Both of these mechanisms, Group C and treatment IND, are formal mechanisms for drugs that are very advanced in their development, usually within months of being marketed.

Over the years, expanded access protocols have also been approved for promising drugs under industry sponsorship, and not at the stage of development that qualifies for a treatment IND. Later, when I describe Dr. Kennealey's presentation, I will discuss one of those programs.

[Slide.]

Now, I will describe single patient use. Basically, with single patient use, the sponsor or physician requests to use drug. The drug supplier decides whether to offer drug for treatment use, the sponsor proposes a plan or a protocol, and then FDA decides whether to allow it.

There are two mechanisms for handling single patient use. In the first mechanism, the single patient IND, a new sponsor files a separate IND, and that sponsor often is an investigator.

In the second mechanism, called the single

patient use exception, there is already an existing IND, there is an existing sponsor, and an investigational protocol. With single patient exception mechanism, a patient who is ineligible for investigational protocol is treated under a plan that usually is a slight modification of the existing protocol. The same IND and the same sponsor are used, and this is a more efficient mechanism for single patient treatment.

Obviously, the single patient mechanism of providing drug is the most laborious for all involved - for the patient, for the physician, the company, and for the FDA. However, this approach does provide the greatest individual oversight, and so it is appropriate for areas where difficult individual judgments must be made.

[Slide.]

So, what are the legal requirements? Legal requirements for single patient use are basically the same as those for any IND. There must be a drug manufacturer that will supply the drug, there must be a sponsor that reports to FDA, there must be an adequately trained investigator, there must be informed consent, and there must be IRB approval. Then, there must be concurrence by

FDA that there is sufficient evidence supporting the drug's efficacy and safety to allow treatment in that individual patient.

[Slide.]

The following are items that FDA considers in evaluating treatment use of experimental drugs: Evidence of drug activity and toxicity, other treatment options for the patient's cancer, whether the sponsor is conducting trials needed for marketing drug, and whether the proposed protocol is likely to interfere with clinical studies needed to approve whether the drug is safe and effective.

In the next slide, I would like to expand on the first two points because these points form the basis for today's FDA questions to the committee.

[Slide.]

The first important question is what evidence do we have about the drug's effect in people. One aspect of this question is to consider the stage of drug development, do we have data from Phase I, Phase II, Phase III studies, and then what do the data show, for instance, what is the response rate and what are the toxicities.

Second, is there effective therapy for the

patient's cancer, and if so, how effective is it. For diseases where there is no standard therapy or where a standard therapy is not satisfactory, FDA has usually permitted single patient use if the data suggest that the treatment is relatively safe.

Evaluating these points requires clinical judgment, and we look forward to the committee's discussion to assist us in making these judgments.

[Slide.]

At our meeting in December, we heard an excellent overview of industry concerns about treatment use of experimental drugs from two physicians who work for pharmaceutical firms - Dr. Robert Spiegel from Schering-Plough and Dr. Gerard Kennealey from Astra/Zeneca Pharmaceuticals. I want to briefly discuss points they made.

[Slide.]

Here are some of the concerns about treatment use of experimental drugs. First, there may be a limited drug supply early in drug development especially with some kinds of drugs. Drugs from these batches are scarce and are very expensive. Then, at some point in development, companies must decide whether the drug is showing enough promise to justify large Phase III studies

and then to convert from small batch manufacturing to large commercial manufacturing.

Before a company converts to commercial production, it may be unreasonable for the oncology community to expect them to provide large amount of drug for treatment use.

Next, there is the concern over competition between expanded access programs and the regulatory programs that will lead to drug approval. Competition can be either for patients entering trials or for internal company resources. Most expanded access programs exclude patients who are eligible for their Phase III regulatory trials to minimize this first concern.

Competition for company resources may occur at multiple levels, for example, in the packaging and shipping departments. The process of individualized packing and shipping of drug for single patient use on an emergent basis can be very disruptive to departments that are organized to pack and ship drug in a scheduled manner for clinical trials.

Another worry is that use in a less controlled setting will lead to more adverse reactions, raising potential safety concerns.

Lastly, industry seems to learn little about drug from single patient use. It is possible that something may be learned from expanded protocols, however.

[Slide.]

Next, Dr. Spiegel shared with us the complexity of the process of single patient use from the daily working experience in a company. First, there is the initial contact where the family or doctor tries to find the right person in the company to begin the dialogue, sometimes involving an extensive process of telephone tag.

Ultimately, the project physician talks to the patient's oncologist. Next, the patient synopsis is submitted, FDA paperwork is submitted, and a protocol must be approved by FDA and by an IRB. Then, there are internal approval steps and the drug must be packaged and shipped.

[Slide.]

In addition, there are follow-up responsibilities including collection of adverse reaction reports, summarizing these adverse reports at intervals for FDA annual reports, and retrieving unused drug. Also, if a patient appears to be benefiting from drug, the company may need to

supply drug to the patients for a prolonged period of time.

So, I think we can see that committing to a program of supplying drug on a patient-by-patient basis is no small step for a company to consider. It could mean commitment of considerable resources.

[Slide.]

Dr. Spiegel suggested that we consider easing the burden of reporting for patients receiving drug under treatment use by only requiring collection of data from unexpected or serious adverse events. In reply, I think this is something that we could consider at times, but it would be on a case-by-case basis.

[Slide.]

The next industry speaker, Dr. Kennealey, addressed expanded access, that is, a procedure that allows multiple patients to be given experimental drug according to a carefully defined protocol.

As suggested by Dr. Kennealey, here are the conditions that may affect whether one needs to consider offering an expanded access protocol. First, when there are early studies in humans showing promising results. Second, in those common

tumors where patients regularly run out of treatment options, and finally, realistically, in circumstances when one expects many requests for treatment use will come in, such as for drugs that are widely discussed in the media.

[Slide.]

Dr. Kennealey described experience with an expanded access program at Astra/Zeneca for a new drug to treat lung cancer, and he offered this as an example of a system that seemed to have worked fairly well.

The first step was to make a commitment, a commitment to the process and to dedicate resources needed to make it succeed. A team dedicated to the project was created. A contract research organization was hired to handle day-to-day matters, such as collecting forms, getting IRB approval, and processing data.

There was careful networking with important parties, such as FDA and advocacy groups. A single informed consent was carefully developed, and an important feature was the determination there would be firm rules about entry with no exceptions made on the basis of persistence or political position.

In order to prevent interference in the process of getting the drug to market, patients were excluded who were eligible for clinical trials that would support FDA approval. Eligibility was restricted to the disease where the most promising activity was shown.

Next, the data collection requirements had to be addressed. In this case, because there were only 300 patients who had been treated with the drug in any trials, the company decided to collect fairly detailed safety data in the expanded access program.

One issue that was not a problem in this particular program was drug shortage, however, this is an important issue that will often need to be addressed.

So, these were the problems addressed in the Astra/Zeneca expanded access experience.

[Slide.]

One of the questions Dr. Kennealey asked FDA to address was how these data from expanded access protocols might be used when the company submits a new drug application and whether these data could decrease the time to NDA submission.

Of course, specifics vary from protocol to

protocol, but these are some of the generalizations I would suggest.

First, the most important data to collect are clearly those on adverse reactions, especially serious events and unexpected new toxicities. Other data are probably seldom very useful in this setting, that is, with a single-arm study where conditions vary widely from patient to patient, and where physicians are less experienced at collecting data and may not have the same support staff for assuring high quality data.

Finally, it does not seem likely that expanded access will speed NDA submission and approval for cancer drugs because usually the rate limiting step in this process is collection of data on effectiveness, data that will usually come from clinical trials. To speed this process, we need more patients in clinical trials.

[Slide.]

However, sometimes it might be reasonable to try to answer some limited questions in expanded access protocols. For instance, sometimes additional populations are treated in expanded access that are not studied in clinical trials, and we can evaluate the frequency of adverse reactions

in this population versus what we have in the clinical trial, or we might consider doing some more simple randomized studies in this setting, comparing two doses of investigational drug where patients could be assured they were getting drug, and evaluating very simple safety or efficacy endpoints, such as survival.

So, that is a summary of the regulatory overview and of the two industry talks that we had from Dr. Spiegel and Dr. Kennealey, and I don't know if we are taking questions now.

DR. NERENSTONE: I think we have time for questions from the committee for Dr. Williams.

[No response.]

DR. NERENSTONE: Thank you very much.

Dr. Taylor will give us a summary of the ethical considerations.

Summary of Ethical Considerations

Sarah Taylor, M.D.

DR. TAYLOR: Good morning. My first statement will be a disclaimer. I am not a medical ethicist, I am a medical oncologist and a palliative care physician dealing a lot with end-of-life issues, so I do deal a lot with ethics.

What I was asked to do was to summarize

what was presented at our last meeting on ethical issues. I have added a few of my own comments because I come to this as a physician, as a patient advocate, and as a family member. My family has had cancer, as well. So, I think you will have to accept a few of my own comments, as well as this summary.

The first speaker was Dr. Sugarman, and he chose to give us a background or a framework for ethics and try to teach us the language of ethics because there are a lot of different words that aren't used in every-day language.

His point was that the off-study use of these experimental drugs was really kind of in-between medical ethics and research ethics. In my own mind, I think research ethics should be basically the same as medical ethics and in many ways they are similar, and we will talk a little bit about that.

If we look at the history of some of medical ethics, which is the first intersection that we have, it goes back, at least the first written word, is with Hippocrates, and which Hippocrates is telling us that we are to do good as physicians.

The Scottish took this a little further in the centuries after that, and they made it a moral obligation that physicians were to be the trustee for the patient and were to hold the good of the patient in their hands and to do good for the patient.

As time went on, life got more complex. We got more machines like dialysis machines. We got more artificial hearts. We got a lot of different complex things, and the idea of doing good for the patient wasn't as easy to define. So, other ways of looking at medical ethics were developed, talked about, and taught.

One of these which he presented was a four-principle look at medical ethics, and he gave four principles that are in this look. The first is autonomy, the second beneficence, the third maleficence, and the fourth is justice.

If you look at the first, which is autonomy, that is our patient right. That is our right to say I don't want treatment. That is our right to say you are not to touch me or give me a treatment without my permission. In a sense, it is a type of informed consent.

The second principle, which is

beneficence, many people feel should be and should remain the first principle, and that is to do good, and that is what we are here for is to help the patient and to do good.

Sometimes that principle in itself can conflict with that autonomy because autonomy means that I define for myself what is good for me, and when we look at beneficence, the physician is having to look at me and try to decide for me what is good, and so there may be conflict within this which leads us to other ethical issues.

Then, if we look at non-maleficence, that is basically what patients expect of us. I think they are very shocked to think that this would even have to be a rule, and that is that we will do no harm. Sometimes that is very complex when you are dealing with seriously ill patients, when you are dealing with very toxic therapies, bone marrow transplants, chemotherapies, and even some of the genetic therapies that can cause death.

Last is justice. Justice is a way of looking at equal access. I think this has been identified in today's talk as a major problem in this off-study use of investigational agents.

So, looking at all of those as our way of

looking at medical ethics, we go on to look at what is research ethics. Unfortunately, instead of those researchers using their medical ethics, our research ethics come out of a lot of scandal.

Unfortunately, there were lots of bad things happened, not just in Nazi Germany, but also in the good old United States in which patients at Tuskegee and elderly patients and retarded patients have had research done on them without the appropriate ethical informed consent.

So, out of this we have come upon various regulatory agencies within our government and within the FDA, we have come up with various rules at looking at research ethics.

One of those summaries has come up with that we will have again three principles, the first being respect for the patient or shall we call it autonomy, the second being beneficence, we are going to do good with the corollary being we won't do bad, and the third being that of justice or looking out for equal access for all patients.

Again, our world has changed, and as science chances, society has changed. Whereas, there was a lot of uproar and upset and feeling that physicians should have protected us from the

thalidomide babies and protected us from being injected with cancer cells on a study without informed consent, more and more you see in society that the patients are demanding more autonomy and in that asking for more access to these new drugs before it is known whether they are effective or not.

Because of that, I think that is why we are having more of these conferences because life is just plain more complex.

I think we are still dealing, and what we have to remember is we are still dealing with vulnerable populations. The vulnerable population is the people that are sick and their families, and they are fighting for their lives, and it is the most vulnerable position we can be in. We are more desperate in those times, more unable to listen and sometimes to understand the complexities of the treatments we are being offered. I think that puts the burden on the physician in terms of again informed consent and communication.

The other aspect that has been alluded to here, that is defined as therapeutic misconception, and I find this a lot in my patient population - well, let's take this experimental treatment, it

must work. If it's experimental, it must be great.

Unfortunately, as a former Phase I researcher, I know that when I wrote those Phase I trials, the objectives of my trials were scientific. I would be wonderfully happy if they also were therapeutic and if my patient responded, but the objectives of the trial were not that of therapy. The objectives of the trial were obtaining a baseline of data about that particular agent, so that I could go on and learn further information about it.

I think that therapeutic misconception is not just a misconception for patients. As you can see by the way we use the terminology, that we are going to use these experimental drugs as treatments. We don't know that they are treatments until they are effective.

I think that what these things hopefully emphasize, the vulnerability and the therapeutic misconception is that we have to do a lot on that autonomy side and providing informed consent. When you are dealing with folks who are sick, that can be very difficult.

Dr. Linden also presented at that meeting in December, and she gave a very nice summary of

her work with a group of activists and to obtaining expanded access to the drug Herceptin. It was a nice history of that, I am not going to go through that.

She made some other important points, I think. Some have been brought up earlier today, and I won't go into a whole lot, but we don't have data in terms of how many people apply, who gets it, why do they get it, and why don't others get it.

I know for a fact from my practice that because I used expanded access protocols, I get a lot of patients whose docs didn't know or wouldn't take the time to go through the process to get an expanded access protocol or to call to get offset use of a drug, so I think that is important that we know the basics, that we know some of the statistics. I am not sure that I know whether we can get all of them, because I do know, it was on the 60 Minute program here, people who know people get drugs in other than the usual fashion.

I think that white paper could then be used as she suggested, to have a conference in which we might try to look at ways to make access easier, to make our systems and our policies

easier, and most importantly, we need to make these systems and policies available in terms of education of the public that they are there.

I know that frequently when I call referring physicians and tell them that these drugs are available if they will just make the call or sign the papers, they are very surprised, so it isn't just a matter of educating parents, it is a matter of educating the public as to what the FDA and the NCI and the drug companies have all made available to us if we will take the time and trouble to do that.

Thank you.

DR. NERENSTONE: Are there any questions from the Committee?

[No response.]

DR. NERENSTONE: Thank you.

Dr. Pelusi will then address the perspective from the patient advocacy community.

Perspective from the Patient Advocacy Community

Jody Pelusi, F.N.P., Ph.D.

DR. PELUSI: Good morning and thank you, Madam Chairman, for allowing me to speak.

I come to you today as the Consumer Rep on the ODAC Committee, and I would like to give you a

little bit of my background because I think that becomes important in terms of how I got a lot of this information and again what I see in my every-day practice.

I am an oncology nurse practitioner with more than 25 years' experience in oncology, mostly in rural settings and in settings with people who are dubbed underserved and minority populations.

I have worked with clinical trials in terms of community clinical trials, and I have also been the family member of numerous family people who have had cancer and have gone through this process as well with them.

[Slide.]

I want to thank all the individuals, organizations, and agencies which shared a lot of thoughts with me and their experiences regarding this issue. Over the last couple months I have been trying to get a lot of input from people to say what do you think about this, because as a consumer rep, we want to represent what the true feelings are in the community.

[Slide.]

What came to mind time and time again and what came up, not only in the presentations that

were given last time by community members, but also this time, as well as all of my interactions, is that we all have the same goal. We have the same goal that all individuals must have equal access to culturally competent, quality cancer care throughout the disease trajectory, and what that means is it includes clinical trials at all phases of the disease process, and it is not just clinical trials in terms of treatment, but also in cancer control and in prevention.

[Slide.]

When we look at what was said last time in December, and we look at what was said today, we hear many different world views, and I just want to go through them and recap what are the themes that we hear, because it makes a difference when we have to decide where do we need to go with this.

What we heard from community is that they wanted the truth about outcome of their disease, and they wanted to know what is known about the new drugs that may be available to them. We need the truth.

People said they did not want false hope from the media or the health care system, but realistic guidance. People stated that they wanted

to know how to make the process of clinical trials and the single patient use program more user-friendly. They wanted to be able to do all that they could individually as a patient and as a family member.

[Slide.]

We also heard that they wanted to have a choice, to take what may be considered a risk, given as much information that was available in relation to the new treatment. People wanted to learn about cancer and treatment options. People want to contribute to society as a whole by being part of the process, and we heard that again today. They want to have a say in the process, and they want the process to be fair and ethical.

[Slide.]

So, when you put all that together and you listen and you listen, clinical trials still are believed to be the very best avenue of obtaining safe and effective treatment. The question becomes do we need more programs to look at single patient use or do we go back before that and say why aren't more people in clinical trials.

When I talked to a lot of individuals, what I heard were the stories about access into

clinical trials, and I think that that is where I want to spend some time this morning sharing with you things that we really need to look at because people really do want to be in clinical trials. People do realize that there is a very, very low rate of participation in clinical trials.

People also believe that the single patient use is necessary in cancer care, but not in all cases, and that there should be criteria. So, let's take a look at the whole issue in terms of clinical trials and how that really impacts this whole issue of should or if we decide about single patient use, things that we really need to consider.

[Slide.]

It seems to be that we really need to look at the system of clinical trials in the process, we need to look at the environment in terms of media, we need to look at health care providers, we need to look at patients and families and communities as a whole.

[Slide.]

In terms of the system, why aren't people in clinical trials? I can tell you from a community person, from a community nurse, this is

very hard because there is delays in the referral process that negates someone's ability to be offered a clinical trial.

With the health care system the way it is set up, with the HMOs, with the plans that are out there, many times people wait two and three months to get referred to even medical oncology. Many times that is past the deadline, if you will, in terms of how long out you can be before you can be eligible for a trial.

I have heard time and time again from many of the research centers we are sitting there waiting, we want to see these patients, we are waiting for approval.

Now, referrals sometimes cannot necessarily be so convenient. I can tell you in a small area, we have four institutions very capable of doing research, they do it all the time, and why are patients being referred two and three hours away to different settings, and it is based on contracts.

Many of our patient who are day workers cannot take off work to drive two and three hours to get the consult to get in the trial, and then on a routine basis, take off time to go down to get

the clinical trial someplace else when it is available right in their own hometown.

The other issue is when are we available, if you will, to give treatments. Many of the patients I work with, I do evening hours, we do weekend hours because our day workers are migrant farm workers, are Native American patients can only come at certain times, and if we are not open, they are not even going to take the treatment, so we really have to look at the process in terms of how do we get and treat patients in a very ethical way in terms of are we really accessible to them.

The referral process may not always be available. Maybe what many people don't realize is when we look at the Indian Health System, there is a whole group of people who don't even have access to referral services.

As you know, the IHS is funded by the Federal Government. Congress decides how much they are going to get. On a regular basis, the last five years, they have been 60 percent funded. That means 40 percent underfunded.

So, if we don't have oncology services within the Indian Health System, that means you have to refer out. If you only have X number of

dollars for referrals, how does that referral get made? Who makes that decision?

We have what we call kind of a life and limb committee that meets on a weekly basis, who gets those dollars and who doesn't.

What is also interesting is you only have and are eligible for referral services if your tribe is in the service unit where the services are being offered, so if you are from Oklahoma and you happen to live in Phoenix, sure, you can come and get all the direct services you want from the medical center there, Indian Medical Center, but if you have to be referred out, you are not eligible for referral services.

So, again, when we look at a population such as Native Americans, and you look to say, sure, they have the lowest incidence of cancer, they also have the highest mortality. When you say who is the most under-represented in clinical trials, it is our Native American population. So, again, it is not that people don't want treatment and don't want to be in trials, it's the process itself.

Then, we look at our uninsured. Many times they are not considered for trial because

there is a perception out there that there will be a lack of compliance. They don't have insurance, they don't have the money that may be required to meet all the requirements in a clinical trial.

[Slide.]

In the system itself, the minority and underserved population, there truly is a disconnect between research and the community. Language barriers, world view barriers, previous history regarding clinical trials, and the time and the resource barriers in making the efforts to get to those communities.

I think that we have to look very closely at this, and so does industry. When we start to look at the development of clinical trials, where is the community voice in the development of that? If you wonder why people have a hard time with informed consents, and you wonder why can't they come on this particular regime, have we looked at the true day-to-day issues?

If we had community members actually helping us design the trials, we are going to have better buy-in. You are going to see people actually talk in their communities about this. Let me give you an example.

I was recently approached by an elders group. The elders group had been asked--they are a group of elderly Native Americans--to look at a clinical trial. It was a prevention trial for prostate cancer.

They were handed, literally handed the trial and said can you look over this. That was their introduction of here, we want you to participate. They came to us, which we are not those particular individuals' health care providers, because we were an Indian System.

What they asked of us, "Is this a good thing or is this a bad thing?" You know, we have kind of been used in the past. We felt uncomfortable with how it was presented to us. What they were asking is we need more education, how do we make good choices about what is out there and about should we partner or not with university settings.

So, it is not that people aren't interested, it is how we approach. So, again, where is this in the very beginning of clinical trials?

[Slide.]

When we look at the media, I can tell you

every person I talked to made a comment about the media, and they made it in a comment of saying we really need to know what the reality is, what are truly the issues, and not sensationalism.

But the other thing that came up time and time again is that many times in the media, what we are seeing is that community is really versing, if you will, either the health care system or, you know, it's the FDA against the community, when, in reality, this is all of us working together for an outcome of better cancer treatments.

So, the question is, is why is that allowed to happen and how again do we partner collectively to address the issue that we are all trying to get to. We cannot be at ends with each other, and we have to really look at that in terms of how do you move forward, and with media having such great access, why not use it to the best of the ability when we talk about education. We can use that medium, if you will, to provide good education about what really exists.

[Slide.]

When we look at health care providers and health care teams, as was mentioned this morning, we all have to look at each one of us and say what

can we do better. Do we truly articulate the disease process? At the time of diagnosis, all we hear is the word "cancer," but do we really understand as time goes by what is going on in terms of disease process, and do we plan for the future.

The question is, is why do we wait until the last minute to say, oh, we need this or we need that? There are very few times when we really don't understand that disease trajectory. We have a pretty good idea from the get-go where are we going with this disease.

If we need time to look at single patient use, we have that time. We also have time to really talk about quality palliative care and end-of-life care. Many patients have been treated, treated, treated, and then we say there is nothing else to give you unless it's an experimental drug. The question is, is there is stuff to give you, and the problem is, is people don't understand that there is excellent palliative care out there, and that is treatment, if you will, for that stage of the disease process.

Do we develop a plan with the patient and family which demonstrates our continued commitment

to care? My question to all of the providers in the room, and I have to ask myself when I see new patients, is do I just give a treatment plan that says we are going to give you this drug, this many times, and how often we are going to give it, or do we really say how are we going to get you through this disease, and it is not just the treatment, it is everything else that goes in.

We need treatment plans that are all-inclusive, if you will, of going through the process, not just one aspect.

[Slide.]

The other question that we have to ask ourselves as providers, if we fail the first-line treatments, do we consider second-line treatment part of clinical trials, how are we determining these outcomes, and that was brought up more and more times to the researchers and to the industry, do we develop from the get-go an arm that looks at those who do not qualify, those patients who may be advanced stage, who have already failed.

I think that has already been mentioned by some of the suggestions, is do we go ahead and already set that criteria upfront, so that there are some guidelines, if you will, or some outcomes

of knowing what are the outcomes in patients who are already advanced or who are different than those who are typically in the clinical trials.

Do we look at the system setting up studies that would already have built in manpower for this or do we need to look at something more globally in terms of a 1-800 number to help screen calls?

When that 60 Minutes program ran, one of the clinic managers called me and said to me I had to bring in another nurse just to man the phones because the phone calls were coming in to their clinic was why didn't I know about this research, why haven't you offered it to me.

So, she had to literally bring in more manpower when indeed, in fact, is there a 1-800 number, so that individuals, physicians can call and say what is available in terms of expanded access, and that that system is really funded by all versus each company having to do it on their own.

Is there screenings that can be set up for such a call center, if you will, to see, indeed, can they move forward to the next step. Again, what I think we have heard, even today, is many

times we get bogged down, if you will, because everybody is doing it individually and it is not being done collectively.

Also, in terms of our rural health providers, and also in our urban settings, maybe we are not educated enough in terms of clinical trials, expanded access, and single patient use. Again, what efforts do we need to make to make sure we all understand, just as Dr. Taylor said, what really is available out there.

Many rural people, especially providers, don't have the time nor the resources to really pursue this process. They may not have the experience to do it either, so the question is an IRB, that doesn't necessarily have to be in one particular place, is there something global that can be done for certain aspects of clinical trials, and I think there is.

When we look at patients and families, I think we really have to look at the whole issue of perceptions, knowledge, beliefs, and values, what are definitions of health and illness, and how does that impact the process.

We have talked before here about quality of life and how that goes into many of our studies,

and we have yet to see that that really is a criteria for studies - do we need to begin to look at that.

The informed consent. Many people have talked about autonomy today and that that is the reason for informed consent, that that person makes the decision. I will challenge you to say that with many people and many people who are coming to this country, it is not an autonomous decision, it is a family decision, and our informed consents are not set up that way.

I can tell you that where I work, it is a family decision. Family members all want to sign the form, and it usually isn't the patient who makes the final decision, it is a consensus decision, and we are going to see more and more people looking at that.

So, we are going to have to look at that, as well, in terms of informed consent. Many patients and families want to be involved in the process, and again, the challenge is when do we involve them.

Many families--and we heard it again today--are responsible for coordinating the care and many times without training or guidance. That

is why people are so passionate about saying I want to do everything I can because they want to make sure they do the very best.

None of us can fault anybody for that, but where is the guidance and where is the training.

[Slide.]

Single patient use. After talking to a lot of people, a lot of agencies, a lot of groups, this is what I heard in terms of general consensus. There needs to be single patient use available for patients who may not have access to routine clinical trials or special circumstantial issues exist.

Again, there are people who could be in clinical trials, but cannot get through the process to get to them. However, there needs to be a single clearinghouse where one can go for information about availability and process.

[Slide.]

What happens--and I have asked this question--what happens when there is standard curable therapy available? People said in their minds the only reason to use single use would be if there was something very specific to an ethical, religious, or circumstantial reason that they could

not undergo such therapies.

[Slide.]

When no standard therapy exists and all previous treatments have failed, this could be considered for single patient use, but all other options need to be explored, and that includes palliative care measures. They need good education, and that is what they are saying, sometimes I don't realize I have anything else or that I don't have to say I have to do something, and that they don't have to feel guilty about not doing something.

Trials initially have set criteria for those individuals. We really need to look at who really gets these, what is their performance status, are they even able to undergo some of these new therapies, and what and when should interventions be started, and what and when should they be stopped.

Many people still feel that when you start something, you have got to keep going, and there are many indications when then is when we do more harm.

We also heard again that nobody wants to interfere with the clinical trials process.

[Slide.]

What about standard therapy when standard therapy provides substantial prolongation, but not curative? People still felt, the majority of people felt that standard therapy really should be utilized, but what needed to be considered is perhaps a cohort to include in that next phase of if indeed that drug was approved and felt to be safe, can we go back and use that group of patients to say they were treated with standard therapy, it wasn't curative, here we are now, can we use it in them.

[Slide.]

So, what we really need and what was really said is we need to address the barriers to the systems of clinical trials itself, the access to the clinical care, the timeliness to referrals, the support of families and providers for this process, more organized approach if we are going to use single use, collaborations with community, media, health care providers, and research, more attention to, if you will, informed consent process, so it is reflective of all communities, and to look at the same in terms of the IRB process.

[Slide.]

Dr. Gil Friedell is somebody who I highly respect. He has done more for the Appalachian poor than anybody else I know, and he always says this at every ICC meeting, Intercultural Cancer Council meeting. He says the issues as well as the solutions come from the community, and I really think that that is true. All of what we are talking about happens at a community level.

[Slide.]

As communities try to address health issues, and they do it by themselves in terms of what expectations are, what they have, we really need to look at all the stakeholders in the community, and we need to sort out roles and responsibilities, and what we are going to find in clinical trials is it is going to vary from community to community, how we get the word out, how we get the buy-in, and we are really going to have to look at it from a community perspective.

Patients are really tired of having people come in and say here, I have this, take it, and not be part of the process. So, we really need to look at community-based education and research.

If you haven't read the article by Israel,

on community-based research, that was published in Public Health in 1999, I would ask every one of you to read that. Community-based research is not an easy thing to do, but it gets us faster to where we want to go, and it means partnering with community, with media, with health care providers from the get-go, and it really means that we have to do community-based outreach in terms of education.

Communities, patients want to be involved and they want to be a partner in the process. They are asking that they get more information, so that they can have a better understanding, and I think we heard this again by everybody that presented this morning. They want to help facilitate the process, they are not here to slow it down.

They want the knowledge. So, whether the researchers come and go, or we come and go as providers, that the community still has the knowledge to carry on in terms of health.

[Slide.]

They were really want to ensure that they are involved in informed consent, and they want the informed consents to be culturally competent. They want the IRB process to be culturally competent, and they want to make sure that all cultures are

reflected in clinical trials.

[Slide.]

So, in summary, our goals are all the same - equal access to culturally relevant, quality cancer care through all stages of the disease, and it has to be a partnership.

Thank you.

DR. NERENSTONE: Does anyone have any questions for Dr. Pelusi?

DR. TEMPLE: Early on, you described the sort of general principle, I guess which would be called justice, that there should be equal access to therapies throughout the development process.

How do you fit that with the observation that the early trials are obviously smaller and more limited? Sometimes justice has been translated to say that people shouldn't be excluded within the community, that they should have access, but you can't have Phase I studies that cover the whole nation or at least not easily.

How do you translate that?

DR. PELUSI: I think what I was referring to, Dr. Temple, is when we look throughout the phases of disease, what I am looking at is do we have even prevention trials available across the

board to people.

When you are looking at Phase I/Phase II, I think the question becomes is if indeed people want to participate, are they going to be able to participate? No, you are not going to be able to have them all around, but is there a system involved that can support that?

So, if indeed you have somebody who wants to be in a Phase I trial, they may not be able to travel to another state to get that, and if insurance, you know, if they don't have insurance, how are they going to be supported to participate?

That is a question that we have to ask ourselves, is there a support system set up that they can participate if they want. Most people really want access, to be really honest what you hear from communities, they want to be able to have what everybody else has in terms of standard of care.

In many communities, standard of care is not available.

DR. TEMPLE: That is sort of what I am asking about. A Phase I study is likely to be done in one or a small number of institutions. The company plainly is not ready to support thousands

of people, and you probably wouldn't want that because you don't know enough about the drug, so how do you translate the equal access to the early stages?

DR. PELUSI: To the early stages of the trials process, again, if you are struggling to get patients into the trials in all phases, and you are especially looking at trying to get minority populations in, you are going to have to support them somehow, and the question becomes are we, if we want people in clinical trials, willing to support them in terms of transportation, in terms of housing for that, and that may be part that has to be built in.

Again, that is the only way we are going to get people into trials, and they are going to have to say, you know, do they even know that they are available. Many people may not want to be in Phase I studies, but do they want to be in Phase II studies, do they want to be in Phase III studies? Perhaps. But again, many people don't participate because they don't have the ability to travel.

Many times it means if you are poor, you don't have access to that if you chose to participate. Many times you don't even know that

that exists.

The question also that goes with that is do they understand what Phase I is, is it something that they want to participate in, have they been educated into what it is that a Phase I study does. You know, are we looking to see is an entity really basically, does it have any activity, what are the potential side effects, not what it is against.

Again, basic education at the community levels can't be done necessarily by us. It needs to be done by community members. I think what you are starting to see, that is coming out in kind of a rough form from some of the special population grants, is that what we are seeing is communities actually want to be the ones that decide how education will be done within their communities, but they want the knowledge from the researchers, they want the knowledge from the experts, if you will, but they want to deliver it in their communities.

So, when you talk about access, again, we have to ask ourselves who do we want in trials, and if we truly say that we want to make sure everybody is represented in trials, we are going to have to say what are the barriers to the trial and did we

build it in, in terms of resources to get people in.

DR. NERENSTONE: Any other questions? Yes, sir.

DR. REDMAN: A question, and it is probably more on the ethical, and maybe Dr. Taylor can respond to this, but I sort of get a sense from some of the community speakers and others that there seems to be--and I guess this deals with patient autonomy, the right to refuse therapy--when or is it an inalienable right that a patient has access to investigational agents? I mean is that written somewhere that everybody has to have access to investigational agents?

DR. TAYLOR: I think if you look at what the write about justice, it is more along the lines of what Dr. Temple alluded to. You have to have, it is felt in our country, and it is certainly not felt in others, that we should all have access to the same medical care when it is relevant, and there are some times when it is not going to be relevant, you are going to not be willing to give your time to fly to California to take a Phase I agent or you are not going to have the disease that it is even reasonable to treat it. You have to set

certain parameters. It is not always relevant that everybody--I don't think that I should be able to demand to go take a Phase I drug as a non-cancer or non-ill patient.

So, I think that you have to look in a relevant way. We don't have equal access to even standard of care in this country, and whether we should or not, only those people that have lots of money are going to be able to tell us because that is where I think it is. We don't have equal access. You see it in your practice every day.

Whereas my patients without insurance may not go in a trial, it may be because they have to keep working, and they can't even come in at night to my 24-hour-a-day clinic because they have to keep working and they can't participate.

So, I don't think there is anywhere that says everybody should get to be on a Phase I trial, but I think that you shouldn't be excluded for other than relevant reasons.

DR. NERENSTONE: We are going to have further discussion after the break. We will take the break now and be back at five after 10:00.

[Recess.]

DR. NERENSTONE: Dr. Taylor has been kind enough to volunteer or was drafted to lead off this discussion.

Sarah.

DR. TAYLOR: We have heard from a lot of different aspects, and I am going to talk to you from my different hats that I wear about this issue. Primarily, I think that we will try to drift back to the off-study use for individual patients as an issue, and not access to medical care, as I was told that is a huge issue.

As a physician, I wear a number of different hats. Number one is I am an oncologist, and as an oncologist, I have a number of cancer patients who come to me today seeking treatments. Issues that I have within my own practice in doing this are that if I am going to use a drug off-label or off-study, that I, number one, have to know about it, and there are a lot of physicians who are not in my position in which I go to meetings and have that luxury of having a group that will cover while I am out trying to learn new information.

I am in a large city where many times the meetings are held. I also have the luxury that I

have a National Cancer Institute grant that pays for data management, and what I manage to do is use that data management to help me keep records of those patients for whom I call and seek the individual INDs or for whom I get expanded access.

Now, if I were an oncologist in private practice, some do belong to community-based research organizations, but many don't, and so as a physician who is not in my position, I would be concerned about the cost, not only my time in terms of calling and arranging it, but my having to pay a nurse to keep the records, pharmacists to mix the drug, all of which I am not going to get any reimbursement for, and I may have to come up with the cost for that.

So, I think that as we talk about these issues, one aspect is the physician side, is cost and time that they have to put into it.

I think that as an oncologist, it is very important that I educate, just as we talked about, in terms of that misconception that because it is an experimental drug, it is going to be better.

With my scientist hat on, I have done an awful lot of studies that were very negative, and I have to say that as a scientist, I look at the

studies and I realize how few responses there are, and I feel that it is important that patients really know that. At one time, the NCI screened 40,000 drugs in a year, and we certainly don't have 40,000 drugs on the market. I think that that is an important part of it.

As a palliative care physician, I have to tell you that many times people come to me with end-of-life issues which should have been addressed far earlier than that last week of life, and that sometimes, as physicians, when we are not willing or able to give the bad news and to give the truth about the fact that the majority of people on a Phase I trial are not going to respond, are not going to have a clinical benefit, and that perhaps you need to look at other issues, such as do you want to go visit your daughter now, should we be looking at other issues in your life.

Hopefully, all of you who do Phase I trials and Phase II trials are controlling that pain anyway. We don't want to be not controlling symptoms, but symptoms need to be controlled. I think that often, as Jody alluded to, people feel that the only treatment has to be an active anti-cancer treatment. Certainly, as a palliative

care physician, I find it very offensive that sometimes my pain and symptom management is not considered treatment because indeed it is a treatment thing.

So, I would hope that as people seek these new agents, that we also keep them well informed about the palliative care issues and the realities of it.

Now, as a patient and a family member, I also understand a number of things in terms of the hope, and I have seen people who weren't supposed to respond to a drug, and that drug isn't on the market respond to a Phase I drug and actually have a complete remission. Those are anecdotes, but they are things that people hold onto and things that keep them looking for other issues. So, I would note that.

I think that another aspect of industry that was not emphasized today, but which I am aware of, is that as they do expanded access on individual patient treatments or use of their drug, they are spending a lot of money, and money may be a real bad word in a lot of ways, but when that industry has to spend that money in that way, I think they have to look at how they are spending it

and whether they are going to get data back that will help the public to know what the drug is going to do and whether it is going to be effective, whether it will be an effective use of their money or whether it will be more money spent that will just increase the cost of the new drugs.

So, I am throwing into the argument here that we have many issues both from industry and physician, and actually from patients who spend a lot of time and effort taking treatment.

DR. NERENSTONE: Dr. Pelusi.

Jody Pelusi, F.N.P., Ph.D.

DR. PELUSI: I was asked to only give four lines. In summary, just to probably hit the four biggest points that I see, is I think that we all hear what people want is to make sure that they get honest, real information about the disease process and about true reality about what is available to treat their cancer. Again, it needs to be inclusive of not only drug therapy, but palliative care.

Also, when we look at this, we hear time and time again nobody wants to slow down the clinical trials process, that we feel that that is the standard, if you will, to truly put effective

and safe drugs on the market.

So, when we begin to look at what should we do with expanded access or special patient use, that in no way do we ever want to slow down the clinical trials process.

Third, we hear that there needs to be education in terms of patients understanding the issue of patient use and expanded use, as well as the medical community.

Fourth, I think that everybody is saying right now, because the system isn't perfect, that single patient use is yes, indeed, something that we need to look at, it may evolve over time, but yet there should be criteria, so that we know that it is safe and effective, and that may be to look at what phase of the study does it become available.

Last but not least, again, people just want access, to be able to say that I am receiving quality care in whatever form that may be.

Thank you.

Committee Discussion

DR. NERENSTONE: I would like to open it up to the committee now for discussion, and I am going to take the chairwoman's prerogative, and I

don't want to reiterate, I think our two leaders made very good and important points. I just want to reiterate very briefly.

One, I think patient education is extraordinarily important and what patients' expectations are of these treatments. It makes me very nervous to hear speakers today talk about experimental treatment as the only potential for cure for their family member.

Most of these drugs are not going to cure anyone. Most of these drugs, even if they are the most effective we can hope, we are talking about increasing people's lives by months, not years, and that is in the most effective drugs that are now used upfront, when they are used in the second, third, and fourth line setting, they have very minimal activity even when we know they are effective.

The other issue is that performance status adherence. I think it is wrong to give patients chemotherapy as they are dying. I think that it is wrong for patients to expect that they should be getting chemotherapy as they are dying.

If patients should not be getting standard therapy because they are no longer of an adequate

performance status, they should certainly not be getting experimental treatment where you know there is no likelihood of any benefit to the patient, and only very severe toxicity.

So, I think these are really very important things for patient education.

Now, I would like to open it up to the rest of the committee.

Dr. Blayney.

DR. BLAYNEY: Thank you. In considering the discussion and reading the material and reviewing what we heard in December, I have four points perhaps in my role as adviser to the FDA.

I think clearly in this country, the autonomy of the patient and that conflict between physician and patient autonomy has been settled on the side of the patient, and I think we all recognize that that is the way things should continue to be and we should respect whenever possible the autonomy of the patient.

Secondly, if we had a frictionless system, we would not be having this discussion today. If the time from a biologic event, meaning giving a drug and observing the effect of that drug, to when that event was recorded, verified, acted upon, and

a decision was made to approve that drug for marketing was very short, this discussion would in large measure be a much smaller issue.

I commend the Agency with the quick approval of Gleevec, and I think not only can that be viewed to your credit, but I would hope that you would learn and work with your drug sponsors and us in the practice community to learn how we can make that more of a common occurrence rather than something that is deserving of comment because it is so out of the ordinary.

Thirdly, I think that in your discussions with PhRMA, you need to encourage them to be proactive and think about a planned access program as part of their drug development process, especially if the sponsor is planning a big media campaign in advance of drug approval, as we have seen with a lot of the drugs that I suspect we will be considering over the next few years, they need to factor an expanded access program into their drug development mechanism.

Second to last, the semantic issue has been touched on. I think the compassionate use needs to disappear from various publications, and also as a semantic issue, I think palliative care

or some other term that is acceptable to patients, you should put into your vocabulary of ways that patients can consider active treatment or compassionate use treatment of experimental agents, that palliative care many times is a much better option for these patients.

Finally, I must say that I am encouraged that the pediatric advocate from whom we heard this morning, and the pediatric, which my understanding is as close to a frictionless clinical trial system as we have, where they have a very high participation in clinical trials in pediatric patients, came to the view, which is largely my view, that the individual use or individual trial should be a mechanism that is used as minimally as possible, so as not to impede drug development.

DR. NERENSTONE: Mr. Erwin.

MR. ERWIN: One thing that seems to come through in a lot of the comments is the need for information, and there has been a focus on patient education, but I think at another level, a more systematic approach to gathering information could be extremely helpful.

We have heard from people with varied experiences in many different types of cancer.

Frequently, there is not a great deal of communication across those interest groups, and the experiences with everything from expanded access in the HIV community to attempts at individual access in certain rare forms of cancer has generated a lot of what is frequently dismissed as anecdotal results.

Given the now almost two decades of history of various types of attempts to gain access to innovative promising new therapies, whether it goes back to early devices or more recent biologics, I think that given that the FDA is going to be a center of focus for a lot of this going forward, it would make sense without it becoming yet another unfunded mandate or some kind of approach to be taken to create a high quality, systematic review of the experience across all of these different disease sectors, and what is the conclusion or conclusions that can be drawn in a much more sort of academic or objective manner in compiling this information and looking at what has worked and what has not worked.

In particular, I think one part of that analysis might be what has worked and what has not worked when it turned out that the device, the

intervention, or the drug was, in fact effective, was ultimately approved, was there benefit in an expanded access program, was there life extension that is statistically valid, was there benefit in even individual access.

There have been some I think important distinctions drawn between expanded access and individual patient INDs, but with all of this discussion of anecdotes, personal histories, emotion, fairness, it seems to me that the overwhelming need for policy decisions or even fair conclusions on justice could benefit a great deal from that kind of a systematic analysis.

DR. NERENSTONE: Ms. Platner.

MS. PLATNER: While there is certainly a consensus in the room that no one wants to undermine the clinical trial system, I don't think that in any way implies that folks wouldn't like to change the clinical trial system and improve the clinical trial system.

I think that looking at the whole issue of single patient INDs, we can go through various scenarios about when it may be appropriate in this circumstance but not that circumstance, and maybe if the situation in this but not that, and I think

in the end, there is no way, no matter what you do with single patient INDs, that you can ever actually make that fair, equitable, or compassionate, and in the end, effective in any way in dealing with the issues that all of these raise.

So, I think it is really time to move beyond that and recognize it as a mechanism that is really not effective and really doesn't work, and look at the clinical trial system itself and how to address issues and maybe look at more trials in late stage disease although in cancer there are many, many trials in metastatic cancer, there are not many trials that deal with later stage disease that look at expanded access, and maybe some other mechanisms for treatments that are very, very promising, and that is not most treatments.

But I think it is really time to move beyond this because in the end, I don't think this mechanism will ever address effectively the issues we want to address, and it just simply will never be fair and equitable.

DR. NERENSTONE: Dr. Temple.

DR. TEMPLE: I just want to provide a little bit of historical background, and it is relevant to these things. One of the reasons the

treatment IND mechanism--and I realize there is some question of whether it should be called treatment IND, but leave that aside--was developed was a perception that the way things were when drugs did look promising, when there was a certain amount of evidence of effectiveness, who got into the various programs of expanded access that existed was capricious and depended on who you knew and whether your doctor was wired in.

The program was designed to make information more widely available, so that it wasn't only for the aficionados and their patients. I have to say to the extent that expanded access--I am talking now about relatively late expanded access--is not using that mechanism and is being sort of local and not using the treatment IND or the Group C equivalent, it is undermining the desire to have it be widely known and fair, and that seems important to me, because one of the things that impressed me most is how infuriating it must be to not know what the rules are for getting whatever you want and being confused about it.

So, whether it should be called something different could be discussed also, but having a public determination that this will be available in

this kind of expanded access in the form of a treatment IND or something like that seems an important part of being fair.

That, of course, doesn't solve the early individual patient problems at all, but I have one thought I wanted to ask people about.

When somebody gets an idea, when a physician gets an idea that a drug might work in a tumor that isn't currently under study, that is a little like a sort of dispersed Phase I study and/or it's a pilot study or something, and while it gets called compassionate use or something else like that, it really seems to me it is more similar to a Phase I study, but of a somewhat different kind.

Those things seem to me less troubling if they are individual because nobody expects that those are going to happen in every part of the country. There will be a certain number of people who, because of interest, want to do something that is not part of the system that the drug company has already set up.

It is when those start to become frequent and numerous--that's the same word--more frequent that you start to get the question of who is

entitled and who is not, and it is at that point that companies ideally would start thinking about whether they want to have a formal program and incorporate this into their trial.

So, it seems important to me to separate, take a try at this tumor that hasn't been studied before with all of the many other circumstances that lead to individual patient uses which do seem to bring questions of capriciousness to the fore.

DR. NERENSTONE: Bob, I don't want to argue semantics with the FDA, but really, don't you mean a dispersed Phase II, because they are not varying the dose, they are just studying it in a different tumor type?

DR. TEMPLE: I will buy that.

DR. NERENSTONE: The only reason I say that, I think the implications are significant because that implies that you have a dose that is being studied in someone in a Phase II manner. It is not a dose that we haven't had some experience with.

DR. TEMPLE: That is fair. I stand corrected. But conceptually, that seems different from the desire for people all over the country to take a last shot in a desperate case and they don't